Renal replacement therapy in support of combat operations

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Background: **Renal replacement therapy has been used by the U.S. Army at the combat support hospital echelon of care since the Korean conflict. Although there has been a general decline in the incidence of wartime acute kidney injury, the mortality associated with acute kidney injury and the use of renal replacement therapy remain unchanged, in the range of 60% to 80%. The U.S. Army official doctrine is that field dialysis is provided through a specialized Hospital Augmentation Team; however, this team has not been deployed to either Iraq or Afghanistan as a result of the ability to rapidly evacuate most cases requiring renal replacement therapy. The history of wartime renal replacement therapy is reviewed along with the general epidemiology of battlefield acute kidney injury and renal replacement therapy.**

Discussion: **Recent literature documents cases of renal replacement therapy performed in and out of theater in support of the current operations. In-theater renal replacement therapy has been provided through a variety of modalities, including conventional hemodialysis, peritoneal dialysis, and both continuous venovenous and continuous arteriovenous hemodialysis. Out of theater, casualties have received both intermittent and continuous hemodialysis at Landstuhl Regional Medical Center and Walter Reed Army Medical Center, whereas patients sustaining burns have undergone aggressive continuous venovenous hemofiltration or hemodiafiltration at Brooke Army Medical Center.**

Summary: **Acute kidney injury requiring renal replacement therapy in wartime casualties is an uncommon occurrence but one with extremely high mortality. Future doctrine should be prepared for contingencies in which the incidence may be increased as a result of mass crush injury casualties or prolonged evacuation times. (Crit Care Med 2008; 36[Suppl.]:S365–S369)**

KEY WORDS: renal replacement therapy; war; acute kidney failure; wounds and injuries; crush syndrome

Military conflicts have played a central role in the development of renal replacement therapy (RRT) since the last half of the 20th century. Intratheater dialysis was first introduced in 1951 during the Korean conflict when Captain Paul E. Teschan of the Walter Reed Army Institute of Research established a renal team near the area of combat capable of providing RRT. Before the availability of dialysis, 84% of those developing posttraumatic renal failure died. After deployment of the renal team, RRT was introduced, and the mortality rate in these patients decreased to 53% (1–3). Teschan later helped establish the Renal Branch at the U.S. Army Surgical Research Unit, Brooke Army Hospital in Fort Sam Houston, TX, and advocated the concept of prophylactic dialysis, initiating dialysis before the development of uremic symptoms (4–6). As a result of the Korean experience, RRT was provided in the Vietnam conflict by both Army field hospitals and U.S. Navy hospital ships (7). In 1975, Conger reported a prospective study of intensive hemodialysis for the treatment of renal failure in Vietnam conflict casualties. Eighteen patients were enrolled in the study and paired according to severity of injury. The "early" intensively dialyzed group (n = 8) was initiated at a mean predialysis serum creatinine of 5 mg/dL, whereas the "late" group (n = 10) was dialyzed at a mean predialysis serum creatinine of 10 mg/dL. Mortality was 36% in the early group compared with 80% in the late group (8).

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Introduction and Historical Overview

Renal failure secondary to combat injuries can be described as a rare complication, albeit one with catastrophic consequences. Although the institution of RRT in the Korean conflict resulted in an apparent decrease in mortality as a result of renal failure, the historical trend in mortality has not appreciably changed over the years. Despite a decrease in all-cause mortality from 22% in Korea to 13% in Vietnam, and a decline in the overall incidence of acute kidney injury (AKI) from 0.5% in Korea to 0.17% in Vietnam, the mortality rates for renal failure reported during Vietnam were unchanged (63% to 70% vs. 68% in Korea) (9). This was in agreement with data from civilian studies showing that use of RRT had not impacted overall mortality (10, 11). The decline in overall mortality and AKI incidence is ascribed to shorter evacuations times (4.6 hrs in Korea vs. 30 to 35 mins in Vietnam) and more aggressive resuscitation strategies (7). The reasons for the unchanged mortality in the face of declining incidence is not clear; it has been suggested that the more modern populations receiving RRT are more severely ill than the historical cohorts, and that renal failure and mortality are associative and not causative. In general, the mortality associated with renal failure remains unacceptably high.

Since Vietnam, the U.S. military has had very little experience with RRT in a combat environment. After the conclusion of the Cold War, the medical support planning called for smaller and mobile medical systems with the main focus on stabilization and rapid evacuation of war-wounded. Specialized resource-intensive support services such as dialysis were eliminated from the core combat hospital

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Table 1. Characteristics of acute kidney injury during military conflicts

Prevalence of chronic kidney disease and conditions increasing risk for acute kidney injury	*U.S./Allied Military:* low *U.S./Allied Civilian:* lower than general population but higher than military *Host Nation Military/Civilian:* closer to general population prevalence, may include end-stage renal disease
Nature of injury	*Non-traumatic:* Volume depletion Medications/Supplements Poisonings Infection-associated Glomerulonephritis *Traumatic:* Direct kidney trauma Direct genitourinary trauma *Posttraumatic:* Crush Ischemia Multifactorial
Evacuation time	Transport availability Patient stability

systems (9). Furthermore, advances in air evacuation of the war-wounded with the emergence of the U.S. Air Force critical care air transport team program in the 1990s has made it possible to rapidly evacuate the most critically ill war casualties out of the theater (12). As such, current U.S. Army doctrine provides RRT capability through supplemental deployment of a Hospital Augmentation Team, Dialysis (HATD), which becomes attached to the combat support hospital when called on (9). The mission of the HATD is to provide the RRT necessary to improve patient stability for transportation out of the theater of operations. The configuration of the HATD consists of one nephrologist, one medical–surgical nurse, and two dialysis technicians plus the dialysis equipment. During the current war in Iraq and Afghanistan, the HATD has never been activated because the need for RRT as a continually available capability has not been identified. However, there have been several cases reported in which acute RRT was provided. (The doctrine and structure for the HATD as well as all other Hospital Augmentation Teams is currently under review by the Army Medical Department Center and School.)

With this perspective, we review the current epidemiology and management techniques for AKI during the current conflicts from the theater of operations to the stateside military hospitals. In addition, the need for deployable RRT capability, for both the current and future conflicts, is reviewed.

Patient Population and Etiology of Acute Kidney Injury

The three primary factors that contribute to the incidence of AKI in a deployed setting are the patient population, the nature of the kidney injury, and the evacuation time to definitive care (Table 1).

The population of patients who could require RRT at the theater hospital (Echelon III) includes U.S. and allied military personnel, allied civilian personnel, and host nation civilian and military personnel. Primary risk factors for the development of AKI from any cause includes preexisting renal disease or conditions such as diabetes mellitus, although our population includes allied military personnel who are relatively young, healthy, and predominantly male. As a result, presumably, these patients have a lower prevalence of chronic kidney disease than the general population as a result of screening before entrance into military service. Conversely, the civilian and host nation populations likely have a more normal prevalence of chronic kidney disease. The U.S. military has provided transient chronic RRT for host nation patients with end-stage renal disease while the host nation infrastructure obtains resources to resume support.

Expected nontraumatic causes of AKI include acute tubular necrosis resulting from a) hypoperfusion/ischemia resulting from the environment and inadequate volume intake; and/or b) toxic injury from medications or dietary supplements. Poisonings may be another nontraumatic indication for RRT, even in the absence of significant AKI. AKI may result as a direct sequela of infections such as malaria or hemorrhagic fever (7). Finally, there is always the possibility of acute glomerulonephritis presenting in the theater in the same way it presents in the civilian world.

Direct trauma to the kidney or genitourinary system is a rare cause of AKI. Therefore, the largest pool of patients requiring RRT can be expected to come from posttraumatic AKI. Of these, crush syndrome deserves special consideration. Crush syndrome, also known as traumatic rhabdomyolysis, occurs as a result of prolonged compression (usually 4–6 hrs) of major muscles in a confined space resulting in direct and indirect (reperfusion) muscle injury (13). Necrosis of skeletal muscle cells and subsequent leakage of intracellular contents into the circulation results in myoglobulinuric AKI with profound, potentially cardiotoxic electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia). AKI is exacerbated further by hypovolemia secondary to fluid sequestration or hemorrhage. The association of renal failure secondary to crush injury was first reported by Bywaters and Beall during the London bombing in 1941. In their report, they described a series of four healthy patients trapped in building rubble who developed shock, limb edema, dark urine, and rapidly progressive uremia with death occurring in all within hours to a few days (14). Over the years, major disasters such as earthquakes have highlighted the prevalence of crush syndrome as an important consideration in medical response planning (9, 13, 15).

The overwhelming predominance of posttraumatic AKI is from multifactorial acute tubular necrosis (ATN). Commonly seen factors include hemorrhage, prolonged hypotension, sepsis, nephrotoxic antibiotics, and radiocontrast dyes. As opposed to crush injury, multifactorial ATN is typically subacute, occurring over the course of several days to weeks.

The final factor in the epidemiology is the time from injury until definitive care can be provided. Lack of available transport and/or patient instability may lead to prolonged evacuation times, which can be expected to increase the risk of hypotension, sepsis, and multisystem organ failure.

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Theater Hospitals (Echelon III)

As expected, the experience of providing RRT at the theater hospital during this war has been limited. As of December 31, 2006, 12 patients required RRT within the Iraqi theater (16). All three military services have played a role in delivering this care. Navy medical personnel provided RRT to three patients (two U.S. active-duty service members, one host nation individual) aboard the United States Naval Ship (USNS) Comfort, a ship-based Echelon IV hospital. Army and Air Force medical personnel provided RRT to nine patients in theater (eight host nation patients, one U.S. active-duty service member) using peritoneal dialysis and continuous renal replacement therapy (CRRT).

The etiology of AKI in this cohort was generally consistent with published reports. Six patients had oliguric multifactorial ATN, five developed myoglobinuric AKI, and one soldier developed renal failure after ingesting ethylene glycol. The age range of those afflicted spanned from a child several months of age to a female of 42 yrs of age. Nine of the 12 patients were male.

Although RRT on board the USNS Comfort mimicked civilian U.S. hospital-based RRT, with single-pass dialysis and portable reverse osmosis systems, the Army and Air Force's experience at the theater hospital level during this war has been different. As a result of the largely unanticipated need for RRT for host nation individuals, no prepositioned dedicated equipment or personnel were in place to manage the eight individuals who required RRT at the theater hospitals and were unstable for transfer to local Iraqi hospitals. (The one exception to this was an early theater hospital, which prepositioned a CRRT machine and used it for the care of one patient.) In the majority of these cases, a nephrologist who happened to be serving as an internist used basic knowledge of CRRT and peritoneal dialysis techniques to devise "field-expedient" methods to deliver these therapies.

A continuous arteriovenous hemofiltration (CAVH) "set" was devised using hemodialysis supplies, filters, and other readily available medical items and was used to successfully perform CRRT on two patients at one Army theater hospital (17). This same system was shared with, and used by, Air Force personnel at another theater hospital on one additional patient requiring RRT.

Peritoneal dialysis (PD) was used in five of eight patients who required RRT at the theater hospital level. As with the CAVH set described previously, some ingenuity was used to create viable sets; pediatric chest tubes were used as PD catheters and dialysate was made using either intravenous saline solution with added bicarbonate and dextrose or Ringer's lactate with D50W added. Ultimately, single- and double-cuffed Tenckoff PD catheters (Kendall Health Care, Mansfield, MA) and line sets were sent from stateside military hospitals to deployed nephrologists along with a video demonstrating catheter insertion.

Outcomes were poor for those who required RRT but mirrored the reported mortality rates of patients with posttraumatic AKI in U.S.-based hospitals. In this series, six of 12 subjects died. All three patients survived who received care on the USNS Comfort with standard acute dialysis equipment, certified dialysis technicians, and a nephrologist all available. At least two of them recovered normal renal function. Of the nine dialyzed at the combat support hospital, six died (three of five in the PD group, two of three in the CAVH group, and one of one in the continuous venovenous hemofiltration group).

Germany (Echelon IV)

At Landstuhl Regional Medical Center (LRMC), RRT had been provided to 16 patients as of December 31, 2006 (16). During the early phases of the war, U.S. military personnel with AKI who were evacuated from the theater to LRMC were transferred to the German civilian medical system if RRT was required. Five patients were managed in this fashion. In late 2004, a rapid-response dialysis team consisting of a nephrologist and dialysis technician from Walter Reed Army Medical Center was created. This team was required to mobilize to LRMC within 18 to 24 hrs after initial contact by intensive care unit medical personnel at LRMC. Later, a full-time active-duty reserve nephrologist stationed at LRMC managed cases of AKI requiring RRT. In total, 11 patients have been treated under the guidance of the mobile dialysis team and/or permanent nephrology personnel stationed at LRMC.

Army Burn Center (Echelon V)

The impact of RRT on military burn casualties with AKI has recently been reported (18). Historically, once AKI is established, the impact on mortality in burn patients is extremely high, between 80% and 100%. Since the beginning of 2003, the Burn Center at the U.S. Army Institute of Surgical Research has admitted nearly 600 military casualties sustaining burns in Iraq and Afghanistan. Before November 2005, only conventional intermittent hemodialysis (IHD) services were available for those who developed AKI. However, critically ill burn patients with AKI are often times not suitable candidates for IHD because AKI commonly develops in conjunction with circulatory shock in these patients. Thus, many of these patients have difficulty tolerating IHD because of hemodynamic compromise. For these reasons, a CRRT program was developed and our first patient was treated in November 2005. Before the CRRT program, a historical control cohort of 16 patients was identified as having >40% total body surface area burns with renal failure (control group); since the start of the program, 18 patients have been treated with CRRT (CRRT group). Of the CRRT patients, seven were treated for isolated acute renal failure, whereas 11 were treated for a combination of acute renal failure and shock. Sixteen of the 18 patients treated were placed on continuous venovenous hemofiltration, whereas the other two were placed on continuous venovenous hemodiafiltration. The dose of therapy was 50.2 ± 13 mL/kg/hr with a treatment course of 5.2 ± 3 days. Interestingly, in the CRRT group treated for shock, eight of 11 had vasopressors discontinued by 24 hrs and the remaining three within 48 hrs. None of the control group patients were placed on RRT. Both 28-day mortality and in-hospital mortality were significantly lower in the CRRT group (22% and 56%) compared with the control group (75% and 88%). Table 2 summarizes our findings. In burn military casualties with AKI, early and aggressive application of CRRT improved survival when compared with a closely matched historical cohort who did not receive renal replacement.

Modalities for Renal Replacement Therapy during Wartime

Various options exist in the civilian world for delivering RRT, but because of

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Table 2. Characteristics and outcomes of burn patients undergoing continuous renal replacement therapy (CRRT) compared with those not receiving renal replacement therapy at Brooke Army Medical Center during Operation Iraqi Freedom

	Control Group (n = 16)	CRRT Group (n = 18)	p Value
Age	30 ± 8	26 ± 3	.06
%Total burn surface area	64 ± 14	68 ± 17	.61
%Full thickness	54 ± 24	58 ± 16	.62
Inhalation injury	12	10	.24
Injury Severity Score	41 ± 16	39 ± 14	1.00
Blood urea nitrogen (T0[a])	55 ± 23	55 ± 21	.98
Creatinine (T0[a])	2.9 ± 1	3.4 ± 1.6	.27
28-day mortality	75%	22%	.002
In-hospital mortality	88%	56%	.04

[a]T0-Day diagnosis of acute kidney injury made (Control) or CRRT initiated.

Table 3. Renal replacement therapy modalities and considerations for use during military conflicts

Modality	Water Requirements per Day	Pros	Cons
Conventional single-pass hemodialysis a. Dialysate via reverse osmosis b. Premade dialysate	a. ~1000 L/day (reverse osmosis) b. ~120 L/day (premade)	• Also capable of CRRT • Effective for highly catabolic patients	• Large water requirements (with machine-generated dialysate) • Storage requirements (with pre-made dialysate) • Special training requirements • Less hemodynamic stability (except in CRRT mode)
Sorbent dialysis	6 L/day	• Water-efficient	• May be less hemodynamically stable than CRRT • Ineffective for some poisonings • Special training requirements • Lack of staff familiarity
Dedicated CRRT machine	Dialysate: 140–720 L/day Replacement fluid: 24–400 L/day	• Hemodynamic stability • Effective for highly catabolic patients	• Need for premade or manufactured replacement fluid and dialysate • Labor-intensive
Continuous arteriovenous hemofiltration	Replacement fluid: 24–48 L/day	• "Low-tech" solution • Hemodynamic stability	• Labor-intensive • Risks of arterial access • Lack of staff familiarity

CRRT, continuous renal replacement therapy.

the austerity of the deployed setting and the nature of battlefield injuries, these options are not equally suitable for the theater hospital. The critical care literature does not support outcomes-based evidence for selection of one modality over another (19). Hence, the doctrine for the U.S. Army has been based on considerations to include water requirements, equipment weight and cube, sturdiness, and training and maintenance requirements.

The single most important logistic factor in performing RRT is the volume of fluid required for dialysate (for hemodialysis and peritoneal dialysis) or replacement fluid (for hemofiltration). As shown in Table 3, with the exception of water-efficient sorbent dialysis systems, the total volume required for treatment may range on the order of 100 to 1000 L per day per patient. Both the dialysate and replacement fluid must be sterile, and no approach for obtaining them is ideal in an austere environment. Single-pass hemodialysis systems make sterile dialysate "on the fly"; however, it must get purified water from a portable reverse osmosis machine, which produces approximately 1 L of purified water for every 10 L of source potable water. Water consumption on this scale in a deployed setting may not be feasible as a general approach. Alternatively, dialysate and replacement fluid may be purchased premade or may be manufactured on-site by modification of stock intravenous solutions, but these approaches require either large storage requirements or are extremely labor-intensive.

The REDY (REcirculating DialYsis) system (Sorb Technology Inc., Oklahoma City, OK) has been the official "warfighting" dialysis machine for the U.S. Army since the 1980s. In addition to its unique system of regenerating and recycling dialysate through the use of a sorbent cartridge, the REDY was compact and relatively simple to maintain. However, commercial manufacture of REDY stopped in 1994 and replacement parts are no longer available. As such, the Army is actively evaluating systems to be the official replacement for the REDY.

The potential options for providing RRT in theater are listed in Table 3. Peritoneal dialysis has the advantages of simplicity and is well tolerated in patients who are hemodynamically unstable or who have elevated intracranial pressures. However, it is relatively contraindicated in patients with abdominal trauma and is inefficient at providing metabolic control for highly catabolic or hyperkalemia patients.

Conventional single-pass dialysis systems are the standard for most RRT performed in the United States. Many modern systems can also be used to perform CRRT or slow low-efficiency daily dialysis. They are extremely effective at controlling catabolic patients. The major disadvantage, as previously mentioned, is the need for a reverse osmosis machine to perform water purification and consequently the large volumes of potable water required.

Dedicated CRRT devices are used in many intensive care units to treat unstable patients or when large ultrafiltration volumes are desired. These usually provide either continuous venovenous hemofiltration or diafiltration. Because of the continuous nature of operation, highly catabolic patients can be controlled. In addition, it may be better tolerated in patients with hemodynamic instability. Disadvantages include labor intensiveness and the large volumes of dialysate and/or replacement fluid that must either be premade or manufactured on-site.

Continuous arteriovenous hemofiltration is an old dialysis technique rarely

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performed today. It is similar in principle to continuous venovenous hemofiltration, but because blood flow is driven by the patient's cardiac output, no special machinery is required. As such, it represents another "low-technology" alternative applicable to hemodynamically unstable patients. Because arterial access is required, this modality must be closely monitored, and special considerations must be given to adequate anticoagulation to keep the dialysis membrane from clotting.

Future Modalities

A potential future alternative is the use of portable single-pass hemodialysis systems such as the NxStage System One (NxStage Medical, Lawrence, MA). The NxStage uses premade fluid and has the additional advantage of being simple in design, dictated by its initial intent for home use, making it ideal for the delivery of RRT in the intensive care unit. This has theoretically obviated the need for specialized dialysis technicians. The tradeoff disadvantage is the resultant larger deployed footprint of the stored fluid.

Newer-generation sorbent dialysis machines such as the Allient (Renal Solutions, Warrandale, PA) provide the same advantages in water efficiency as the REDY and may provide to be a suitable replacement. The Allient is also designed for home use and as such also has the same advantages in this regard as the NxStage System One. The disadvantages include the unfamiliarity of most clinicians of the principles of sorbent dialysis. The experience of newer sorbent dialysis devices in providing CRRT-like therapy is unknown. Sorbent dialysis is also ineffective in treating several of the common poisoning indications for conventional dialysis, for example, methanol, ethylene glycol, and lithium.

Summary

RRT in support of current combat operations has been provided through a variety of modalities, including single-pass hemodialysis, peritoneal dialysis, continuous venovenous hemofiltration, and CAVH. These are augmented by the availability of RRT at higher echelons of care out of the theater.

The low number of cases requiring RRT in Iraq and Afghanistan do not indicate the need for a deployed RRT capability in the present conflict. It is likely that the capability to rapidly evacuate even the most severely injured casualties out of the theater, before AKI can ensue, has had an impact. It is also not clear whether there is also a lower total incidence of AKI or of a lower proportion of AKI leading to RRT. This epidemiologic information, specifically the overall incidence of AKI at all echelons of care and the associated mortality, is a priority being pursued by the Nephrology Consultant to the Office of the Surgeon General of the Army.

A doctrinal question is whether the current lack of need for in-theater RRT is an indication that it will no longer be a required capability for the U.S. Army in future missions. Future deployments may encounter more significant numbers of casualties with crush injuries such as in urban conflicts or in humanitarian missions in response to natural disasters. Progression of myoglobulinuric AKI may require use of RRT as early as the first 1 to 3 days for metabolic stability (20). Additionally, the current short transport times from injury to a combat support hospital to Germany are best-case scenarios, and deployable RRT would be a contingency against more prolonged evacuations.

The significant number of host nation patients who cannot be evacuated and who require RRT is an issue that had not been fully appreciated until the present operations. The solutions to providing acute and chronic RRT for host nationals is a matter to be considered in a future doctrine.

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